

**Amendments to the Claims**

Please amend Claims 57, 59, 60, 73 and 74. The Claim Listing below will replace all prior versions of the claims in the application:

**Claim Listing**

Claims 1-56 (Canceled)

57. (Currently Amended) A method of identifying a compound which covalently binds to the surface of a target protein in sufficient proximity to the binding site between a macromolecular ligand and the target protein to inhibit binding of the macromolecular ligand with the target protein, said method comprising the steps of:

- a) selecting a lead compound which non-covalently binds to the surface of a target protein with a  $K_d$  of greater than about 0.10  $\mu\text{M}$ , wherein said lead compound is represented by the structural formula T-H;
- b) preparing a plurality of analogs of the lead compound, each analog being represented by the structural formula T-L-A, wherein L is an inert linking group, A is a moiety comprising a reactive functional group and -L-A, taken together, is different for each analog;
- c) combining the target protein, macromolecular ligand and each analog under conditions suitable for covalent binding between the target protein and macromolecular ligand;
- d) assaying each combination of step c) for inhibition of macromolecular ligand/target protein binding and for covalent binding between the analog and the target protein; and
- e) selecting analogs which inhibit macromolecular ligand/target protein binding and which covalently bind with the target protein.

58. (Previously Presented) The method of Claim 57 wherein the lead compound inhibits binding of the macromolecular ligand with the target protein.

59. (Currently Amended) The method of Claim 58 additionally comprising the steps of:
- a) preparing a plurality of additional analogs of an analog selected in step e);
  - b) combining the target protein, macromolecular ligand and each additional analog under conditions suitable for binding between the target protein and macromolecular ligand;
  - c) assaying each combination of step g) for inhibition of macromolecular ligand/target protein binding and for covalent binding between the additional analog and the target protein; and
  - d) selecting additional analogs with ~~improved~~ increased inhibition of macromolecular ligand/target protein binding compared with the analog selected in step e).
60. (Currently Amended) The method of Claim 59 additionally comprising the step of repeating steps f)-h) with an analog selected in step i) and selecting analogs with ~~improved~~ increased inhibition of macromolecular ligand/target protein binding compared with the analog selected in step i).
61. (Previously Presented) The method of Claim 58 wherein the lead compound is selected by screening a combinatorial library of compounds for inhibition of target protein/macromolecular ligand interaction.
62. (Previously Presented) The method of Claim 58 wherein the complex between the target protein and macromolecular ligand is modeled computationally, by x-ray crystallography; by nuclear magnetic resonance spectrophotometry or by active site localization; the target protein/macromolecular ligand binding site is identified from the model(s); and wherein a lead compound is designed based on its ability to bind to the protein target/macromolecular ligand binding site.

63. (Previously Presented) The method of Claim 58 additionally comprising the steps of:
- a) modeling the complex between the target protein and the lead compound computationally, by x-ray crystallography; by nuclear magnetic resonance spectrophotometry or by active site localization;
  - b) identifying reactive functional groups on the surface of the target protein in the vicinity of the binding site between the target protein and lead compound; and
  - c) selecting A groups that can form covalent bonds with the reactive functional groups on the surface of the protein; and
  - d) selecting L groups that will bring the A groups into sufficient proximity with the reactive functional groups on the surface of the protein to covalently react after binding between the targeting group and the target protein.
64. (Previously Presented) The method of Claim 58 wherein the reactive group has a reactivity with the corresponding free amino acid under physiological conditions of less than about  $10^{-4} \text{ M}^{-1}\text{sec}^{-1}$ .
65. (Previously Presented) The method of Claim 58 wherein the linking group is inert.
66. (Previously Presented) The method of Claim 58 wherein said linking group is cleavable *in vivo*.
67. (Previously Presented) The method of Claim 58 wherein the targeting group is degradable *in vivo*.
68. (Previously Presented) The method of Claim 66 wherein the compound has an *in vivo* half-life of at least about one minute.
69. (Previously Presented) The method of Claim 67 wherein the compound has an *in vivo* half-life of at least about one minute.

70. (Previously Presented) The method of Claim 64 wherein the targeting group is a carbohydrate, natural product, peptide, protein, antibody or monoclonal antibody.
71. (Previously Presented) A method of identifying a compound which covalently binds to the surface of a target protein in sufficient proximity to the binding site between a macromolecular ligand and the target protein to inhibit binding of the macromolecular ligand with the target protein, said method comprising the steps of:
- a) selecting a lead compound which non-covalently binds to the surface of a target protein, wherein said lead compound is represented by the structural formula T-H;
  - b) preparing a plurality of analogs of the lead compound, each analog being represented by the structural formula T-L-A, wherein L is a linking group, A is a moiety comprising a reactive functional group, -L-A, taken together, is different for each analog and the linking group is cleavable *in vivo* or the targeting group is degradable *in vivo*;
  - c) combining the target protein, macromolecular ligand and each analog under conditions suitable for binding between the target protein and macromolecular ligand;
  - d) assaying each combination of step c) for inhibition of macromolecular ligand/target protein binding and for covalent binding between the analog and the target protein; and
  - e) selecting analogs which inhibit macromolecular ligand/target protein binding and which covalently bind with the target protein.
72. (Previously Presented) The method of Claim 71, wherein the lead compound inhibits binding of the macromolecular ligand with the target protein.

73. (Currently Amended) The method of Claim 72, additionally comprising the steps of:
- a) preparing a plurality of additional analogs of an analog selected in step e);
  - b) combining the target protein, macromolecular ligand and each additional analog under conditions suitable for binding between the target protein and macromolecular ligand;
  - c) assaying each combination of step g) for inhibition of macromolecular ligand/target protein binding and for covalent binding between the additional analog and the target protein; and
  - d) selecting additional analogs with ~~improved~~ increased inhibition of macromolecular ligand/target protein binding compared with the analog selected in step e).
74. (Currently Amended) The method of Claim 73 additionally comprising the step of repeating steps f)-h) with an analog selected in step i) and selecting analogs with ~~improved~~ increased inhibition of macromolecular ligand/target protein binding compared with the analog selected in step i).
75. (Previously Presented) The method of Claim 72 wherein the lead compound is selected by screening a combinatorial library of compounds for inhibition of target protein/macromolecular ligand interaction.
76. (Previously Presented) The method of Claim 72 wherein the complex between the target protein and macromolecular ligand is modeled computationally or by x-ray crystallography; the target protein/macromolecular ligand site is identified from the model(s); and wherein a lead compound is designed based on its ability to bind to the protein target/macromolecular ligand binding site.

77. (Previously Presented) The method of Claim 72, additionally comprising the steps of:
- a) modeling the complex between the target protein and lead compound computationally, by x-ray crystallography; by nuclear magnetic resonance spectrophotometry or by active site localization;
  - b) identifying reactive functional groups on the surface of the target protein in the vicinity of the binding site between the target protein and lead compound; and
  - c) selecting groups that can form covalent bonds with the reactive functional groups on the surface of the protein; and
  - d) selecting L groups that will bring the A groups into sufficient proximity with the reactive functional groups on the surface of the protein to covalently react after binding between the targeting group and target protein.
78. (Previously Presented) The method of Claim 72 wherein the compound has an *in vivo* half-life of at least about one minute.
79. (Previously Presented) The method of Claim 72 wherein the linking group is inert.
80. (Previously Presented) The method of Claim 78 wherein the compound has a molecular weight greater than about 1500 amu.
81. (Previously Presented) The method of Claim 78 wherein the targeting group binds non-covalently to a surface of the target protein with a  $K_d$  of greater than about 0.10  $\mu\text{M}$ .
82. (Previously Presented) The method of Claim 81 wherein the reactive group has a reactivity with the corresponding free amino acid under physiological conditions of less than about  $10^{-4} \text{ M}^{-1}\text{sec}^{-1}$ .
83. (Previously Presented) The method of Claim 81 wherein the targeting group is a carbohydrate, natural product, peptide, protein, antibody or monoclonal antibody.

84. (Withdrawn) A compound for inhibiting binding between a target protein and a macromolecular ligand of the target protein, said compound comprising a targeting group and an attaching group, wherein:
- the targeting group is a moiety that binds non-covalently to a surface of the target protein with a  $K_d$  of greater than about 0.10  $\mu\text{M}$  and within sufficient proximity to the target protein/macromolecular ligand binding site such that the compound inhibits binding between the target protein and the macromolecular ligand; and
- the attaching group is a moiety comprising a reactive functional group which can form a covalent bond with an amino acid on the surface of the target protein after the targeting group binds with the target protein.
85. (Withdrawn) The compound of Claim 84 wherein the reactive functional group has a reactivity with the corresponding free amino acid under physiological conditions of less than about  $10^{-4} \text{ M}^{-1}\text{sec}^{-1}$ .
86. (Withdrawn) The compound of Claim 84 additionally comprising an inert linking group which connects the targeting group with the attaching group.
87. (Withdrawn) The compound of Claim 84 additionally comprising a linking group which connects the targeting group with the attaching group, wherein said linking group is cleavable *in vivo*.
88. (Withdrawn) The compound of Claim 84 wherein the targeting group is degraded *in vivo*.
89. (Withdrawn) The compound of Claim 87 wherein the compound has an *in vivo* half-life of at least about one minute.
90. (Withdrawn) The compound of Claim 88 wherein the compound has an *in vivo* half-life of at least about one minute.

91. (Withdrawn) The compound of Claim 84 wherein the compound has a molecular weight greater than about 1500 amu.
92. (Withdrawn) The compound of Claim 91 wherein the targeting group is a carbohydrate, natural product, peptide, protein, antibody or monoclonal antibody.
93. (Withdrawn) A compound for inhibiting binding between a target protein and a macromolecular ligand of the target protein, said compound comprising a targeting group, an attaching group and, optionally, a linking group, wherein:
- the targeting group is a moiety that binds non-covalently to a surface of the target protein and within sufficient proximity to the target protein/macromolecular ligand binding site such that the compound inhibits binding between the target protein and the macromolecular ligand;
  - the attaching group is a moiety comprising a reactive functional group which can form a covalent bond with an amino acid on the surface of the target protein after the targeting group binds with the target protein;
  - the linking group connects the targeting group and the attaching group; and
  - the targeting group is degradable *in vivo* or the linking group is cleavable *in vivo*.
94. (Withdrawn) The compound of Claim 93 wherein the compound has an *in vivo* half-life of at least about one minute.
95. (Withdrawn) The compound of Claim 94 wherein the compound comprises an inert linking that connects the targeting group and attaching group.
96. (Withdrawn) The compound of Claim 94 wherein the compound has a molecular weight greater than about 1500 amu.
97. (Withdrawn) The compound of Claim 96 wherein the targeting group is a carbohydrate, natural product, peptide, protein, antibody or monoclonal antibody.



98. (Withdrawn) The compound of Claim 94 wherein the targeting group binds non-covalently to a surface of the target protein with a  $K_d$  of greater than about 0.10  $\mu\text{M}$ .
99. (Withdrawn) The compound of Claim 98 wherein the reactive functional group has a reactivity with the corresponding free amino acid under physiological conditions of less than about  $10^{-4} \text{ M}^{-1}\text{sec}^{-1}$ .
100. (Withdrawn) A method of inhibiting binding between a target protein and a macromolecular ligand in a subject in need of such inhibition, said method comprising the step of administering to the subject an effective amount of a compound comprising a targeting group and an attaching group, wherein:
- the targeting group is a moiety that binds non-covalently to a surface of the target protein with a  $K_d$  of greater than about 0.10  $\mu\text{M}$  and within sufficient proximity to the target protein/macromolecular ligand binding site such that the compound inhibits binding between the target protein and the macromolecular ligand; and
- the attaching group is a moiety comprising a reactive functional group which can form a covalent bond with an amino acid on the surface of the target protein after the target group binds with the target protein.
101. (Withdrawn) The method of Claim 100 wherein the reactive functional group has a reactivity with the corresponding free amino acid under physiological conditions of less than about  $10^{-4} \text{ M}^{-1}\text{sec}^{-1}$ .
102. (Withdrawn) The method of Claim 100 additionally comprising an inert linking group which connects the targeting group with the attaching group.
103. (Withdrawn) The method of Claim 100 additionally comprising a linking group which connects the targeting group with the attaching group, wherein said linking group is cleavable *in vivo*.

104. (Withdrawn) The method of Claim 100 wherein the targeting group is degraded *in vivo*.
105. (Withdrawn) The method of Claim 103 wherein the compound has an *in vivo* half-life of at least about one minute.
106. (Withdrawn) The method of Claim 104 wherein the compound has an *in vivo* half-life of at least about one minute.
107. (Withdrawn) The method of Claim 100 wherein the compound has a molecular weight greater than about 1500 amu.
108. (Withdrawn) The method of Claim 107 wherein the targeting group is a carbohydrate, natural product, peptide, protein, antibody or monoclonal antibody.
109. (Withdrawn) A method of inhibiting binding between a target protein and a macromolecular ligand in a subject in need of such inhibition, said method comprising the step of administering to the subject an effective amount of a compound comprising a targeting group and an attaching group, wherein:
- the targeting group is a moiety that binds non-covalently to a surface of the target protein and within sufficient proximity to the target protein/macromolecular ligand binding site such that the compound inhibits binding between the target protein and the macromolecular ligand;
  - the attaching group is a moiety comprising a reactive functional group which can form a covalent bond with an amino acid on the surface of the target protein after the targeting group binds with the target protein;
  - the linking group connects the targeting group and the attaching group; and
  - the targeting group is degradable *in vivo* or the linking group is cleavable *in vivo*.
110. (Withdrawn) The method of Claim 109 wherein the compound has an *in vivo* half-life of at least about one minute.

111. (Withdrawn) The method of Claim 110 wherein the compound comprises an inert linking group that connects the targeting group and the attaching group.
112. (Withdrawn) The compound of Claim 110 wherein the compound has a molecular weight greater than about 1500 amu.
113. (Withdrawn) The method of Claim 112 wherein the targeting group is a carbohydrate, natural product, peptide, protein, antibody or monoclonal antibody.
114. (Withdrawn) The method of Claim 110 wherein the targeting group binds non-covalently to a surface of the target protein with a  $K_d$  of greater than about 0.10  $\mu\text{M}$ .
115. (Withdrawn) The method of Claim 114 wherein the reactive functional group has a reactivity with the corresponding free amino acid under physiological conditions of less than about  $10^{-4} \text{ M}^{-1}\text{sec}^{-1}$ .